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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,081	04/05/2006	Olli Vuolteenaho	50635/002001	9413

21559 7590 10/06/2010

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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
10/06/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/562,081	**Applicant(s)** VUOLTEENAHO ET AL.	
	Examiner SHULAMITH H. SHAFER	**Art Unit** 1647	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 September 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 112, 1st, enablement and written description.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-4,7-10,12-17 and 62-68*.
   Claim(s) withdrawn from consideration: *29-37 and 40-44*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See below.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Shulamith H. Shafer/
Examiner, Art Unit 1647

The amendment submitted on 7 September 2010 will be entered. Claims 1-4, 7-21, 23-37, 40-44, 46, 47, 49-52, 60 and 62-68 apre pending in the instant application. Claims 28-37 and 40-44 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. In the original response to requirement for election of species (Response of 10 July 2008), applicants elected the following species: SEQ ID NO:3 (NT-proANP), SEQ ID NO:6 (NT-proBNP), Claims 11, 18-21, 23-27, 46-52, 59 and 60 are canceled.
Claims 1-4, 7-10, 12-17, and 62-68 are under consideration to the extent they read on the elected invention.

Claims 11, 18-21, 23-27, 46-52, 59 and 60 are canceled. All objections and rejections of these claims are thereby moot.

The rejection of Claim 3 which depend from Claim 1, under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps is maintained for reasons of record and for reasons set forth below. See MPEP § 2172.01. Claim 1 is directed to a method of determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject. Claim 3 recites contacting the sample with a fusion polypeptide agent comprising both proANP and pro-BNP and contacting the sample with a binding substance which is able to bind to pro-ANP and proBNP and a fusion polypeptide comprising both proANP and pro-BNP. However, the claims do not require the fusion polypeptide agent or fusion peptide agent to be labeled in any way that would allow one of ordinary skill in the art to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1, and the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of the presence of the fusion polypeptide. While the claim recites contacting steps, it fails to explicitly recite method steps directed to detection of the atrial and brain natriuretic peptide prohormones that are present in the sample and distinguishing said peptides from the added agent. Thus, performing the steps of the claimed method would not achieve the stated goal, which is determining activation or inactivation of the atrial natriuretic peptide and brain natriuretic peptide hormonal systems by detecting the presence or amount of proANP and proBNP in a sample from the subject.

Applicants traverse the rejection (remarks of 7 Sept. 2010, page 13, 3rd paragraph, bridging page 14, 1st paragraph). The reason for the traversal is:

Applicants submit that recitation of a functional limitation for the claimed fusion polypeptide is sufficient to render the claim term definite. One skilled in the art at the time of the invention would have understood the nature and role of a "calibration agent" or "competitive inhibitor" without recitation of a particular structural feature (e.g., a detectable label). Furthermore, one skilled in the art at the time of the invention would have been able to readily conceive of embodiments of the claimed invention that included,
Applicant's arguments have been fully considered but are not found to be persuasive reasons of record:
Absent any recitation that the fusion polypeptide or peptide is labeled in some way that would distinguish the calibration agent or competitive inhibitor from the proANP or proBNP that is present in the sample to be tested, one would not be able to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1, and the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of the presence of the fusion polypeptide.
Claism 4 and 9 are included in the rejection, as dependent upon Claim 3.

The rejection of Claims 1, 16, 17, 62-66 and 68 under 35 U.S.C. 103(a) as being unpatentable over Clerico et al (1998. J Endoc. Invest 21:170-179), in view of Clerico et al. (2000. Clin. Chemistry 46:1529-1534) is maintained for reasons of record, as set forth below.
Clerico et al (1998) teach measurement of plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels in plasma of patients with heart failure as an assay method useful in follow-up of cardiac patients (monitoring a cardiac condition) (abstract). The measurements are performed on plasma samples from healthy human subjects and patients with chronic cardiomyopathy (page 172, 1st column, 2nd paragraph). The measurements from healthy, normal subjects in the general population were used to establish a reference level of normal ANP and normal BNP levels (Figure 3). Both polypeptides were measured in samples from the same subject (page 174, 1st column, 3rd paragraph and page 175, 2nd column, last paragraph); absent evidence to the contrary, said measurements would constitute simultaneous detection. The measurements were performed using non-competitive immunoradiometric assays (IRMA) (page 172, 1st column, last paragraph bridging page 173, 2nd column, 1st paragraph). The reference teaches utilizing standard solutions comprising known quantities of ANP and BNP to generate standard curves which act as reference values to determine the amount of ANP and BNP in the samples from patient subject (Page 172, 2nd column, 2nd paragraph and page 173, 1st column, 1st paragraph). While the reference does not teach determining a reference level from a previous measurement from the same subject, the reference does teach that the assay methods for these peptides may be useful in the follow-up of cardiac patients, thus teaching the advantage of comparing the detected level of the natriuretic peptides in one assay to those detected in a sample from the same patient in a previously performed assay.
Clerico et al (1998) does not teach a method comprising detecting the presence of atrial and brain natriuretic peptide prohormones or fragments thereof. Clerico et al (2000) teach that cardiac natriuretic hormones are a family of related peptides including ANP, BNP and other peptides derived from the N-terminal portion of proANP and proBNP peptide chains (abstract). The reference teaches that the N-terminal prohormones (NT-proANP and NT-proBNP) are present in greater amounts in the plasma than ANP and BNP (Table 1).
It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Clerico et al (1998) and substitute measurement of proANP and proBNP (as taught by Clerico et al (2000)) for the measurement of ANP and BNP as taught by Clerico et al. (1998). The person of ordinary skill in the art would have been motivated to make these modifications because Clerico et al (2000) teach that the prohormones are present in higher concentrations in the plasma and one of ordinary skill in the art would recognize that these may be measured more easily and accurately. One would reasonably have expected success because methods of measuring said prohormones are outlined by Clerico et al (2000).
Additionally, one of ordinary skill, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays (for example, a lipid profile, liver enzyme assays), would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Techniques utilizing immunoassays for simultaneous detection of two polypeptides in a single reading in a single assay were well known at the time of the instant invention, as evidenced by

Swartzman et al which teaches simultaneous detection of two cytokines, IL-6 and IL-8 in the same high-throughput multiplexed immunoassay. (See, for evidentiary purposes only, Swartzman et al. 1999. Analytical Biochem. 271:143-151, abstract)
Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample.
With respect to the limitations recited in Claims 65 and 66. While the references do not teach assays calibrated so that a particular reading in the assay is know to represent the normal peptide level (Claim 65) or assays wherein the assay is calibrated so that a normal level will produce a negligible or insignificant result (Claim 66), one of ordinary skill in the art is aware that calibration of read-out instruments, such as FACs machines or counters which detect radioactivity, to set base-line levels at pre-determined, desired levels is routine in the art of immunoassays
Applicants traverse the rejection (page 15, 2nd column bridging page 18, 1st paragraph. The reasons for the traversal are:

By suggesting that Swartzman is relevant to the claimed invention, the Examiner appears to conflate the claim term "a single reading" with the claim term "a single assay." While Swartzman does describe an assay for measuring IL-6 and IL-8 simultaneously in a single assay, each cytokine produces a separate reading (see, e.g., figure 4A, which shows the average fluorescent intensity corresponding to IL-6 in grey bars and IL-8 in white bars).
Furthermore, Applicants respectfully request that the Examiner again consider the limitation that the claimed method does not include detection of the proteins "individually." The Examiner does not cite a publication teaching the claim limitation that proANP and proBNP not be measured individually, because Swartzman, Clerico (1999), and Clerico (2000) all describe the individual measurement of separate analytes (e.g., ANP and BNP). Particularly in view of the claim limitation that the proteins be detected in a single reading and not individually, Applicants respectfully submit the invention of claim 1 would not have been obvious over the cited art.

Neither Clerico reference teaches that it would have been useful to measure both proANP and proBNP without distinguishing between the two proteins.
Applicant's arguments have been fully considered but are not found to be persuasive for reasons of record.
While the Cicero references do not teach detection of both natriuretic peptides without the detection of the presence of proANP or proBNP individually such ideas flow naturally from the teachings of the prior art. One of ordinary skill, aware of the teachings of the cited references, and in the interests of efficiency could easily design such an assay: for example by labeling an antibody to pro-ANP and an antibody to pro-BNP (a mixture of mono-specific binding substances) with the same detectable label. By doing so, one would detect both proteins in the same reading. Absent evidence that assaying for one protein, i.e. detection of ANP, would interfere with the detection of the second protein, i.e. detection of BNP, one of ordinary skill would anticipate success in detecting both proteins simultaneously in the same sample.

A central feature of the present invention is the detection of the presence of both proANP and proBNP-related sequences in a single reading, in a single assay. Also as discussed above, it would not have been obvious in view of either Clerico reference to perform a single assay to obtain a single reading that determines the presence of proANP and proBNP, without distinguishing between the two polypeptides. Buechler ('838) does not add what is missing from the Clerico references in supporting this rejection, as Buechler (' 838) does not teach or suggest testing for the presence of proANP and proBNP-related sequences in a
reading, in a single assay.
Applicants arguments have been fully considered but are not deemed to be persuasive for reasons of record and for reasons discussed above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.